Drugs and Air Operations

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INTRODUCTION

There can be little doubt that the performance of air personnel may deteriorate during intensive and sustained operations, and much thought has been given to the use of hypnotics to preserve sleep, and stimulants to enhance vigilance. The effect of these two possibilities may be complementary. Stimulants may be particularly useful for critical periods of work likely to involve impaired performance when used against a background of hypnotics to ensure adequate sleep in limited rest periods. However, the use of hypnotics and stimulants demands the most careful evaluation of each individual drug, and of their interactions.

In the case of hypnotics the overriding consideration, assuming efficacy, is duration of action which is dependent on the dose and the pharmacokinetic profile. Determination of the minimal dose is essential. Information on the pharmacokinetic profile is useful, though it is not possible to predict duration of action from such data with any certainty. It is often implied that the elimination half-life determines the duration of action, but duration of action also depends on rate of absorption and distribution, and so all three phases of the pharmacokinetic profile, as well as the minimum effective concentration for a particular effect, are involved. It is essential to carry out experimental studies to determine the minimum dose to produce sleep during a limited period of rest, and to ensure that impairment of performance does not extend into the work period.

In the use of stimulants attention must be given to the effect of the drug on performance as well as duration of action. It is vital to ensure that adverse effects on performance do not arise from the use of a stimulant, and for this reason a wide range of performance tasks must be included in the assessment. Dose is important, and the minimum dose necessary to maintain performance over the period of work must be determined. As with hypnotics studies must be carried out to determine duration of action to ensure that the use of a stimulant does not adversely affect the ability to sleep in the subsequent rest period, which may be critical in maintaining the continued effectiveness of the individual.

There are two broad approaches to studying the activity of hypnotics and stimulants to predict the effect which they may have on the performance of the individual. The profile of activity can be built up by using a variety of laboratory tests directed toward assessing specific skills relevant to the work of the individual, or the task itself can be simulated with as much accuracy as possible. Inevitably the question arises whether information obtained with performance tests carried out in the laboratory are relevant to day-to-day work. At first sight simulation maybe a more attractive approach, but there are serious doubts whether simulation provides data more relevant to the real situation. It is beyond discussion that laboratory studies provide accurate information on discrete skills and on persistence of effect, and it is, therefore, essential that simulation provides data of at least equal value.

It is true that studies using simulation may bring increased reality and motivation to the experimental set-up. However, uncertain or insensitive measures have no advantage over accurate measures from the laboratory. Simulators may merely test isolated functions in a complex, expensive and possibly uncontrolled way. Spurious confidence in the use of simulation must be avoided. Nevertheless, there is a measure of agreement between studies using simulation and laboratory tests, and it is the contention that laboratory tests do not provide such useful information as simulation which is in dispute. At present, laboratory tests remain essential, though the development of the means to measure more sophisticated skills, such as hazard perception using simulators, is welcome. Studies

using laboratory tests, hand in hand with simulation, provide the ideal approach.

Whatever the approach, change in performance needs careful interpretation as the central nervous system itself is modified. Other skills which may be of greater relevance to the task than those actually tested may be affected. On the other hand, an inability to demonstrate impaired performance does not necessarily mean a drug is free of adverse effects, as there is no test or group of tests which would indicate that human performance is preserved. It is, therefore, essential that a wide variety of data is considered in the use of hypnotics and stimulants in air operations, and that the operational scenario is well understood to ensure that these drugs will be used both effectively and safely.

As far as the use of such drugs is concerned, it must be appreciated that the overriding feature of some air operations may be several days of continuous action in an attempt to overcome defences or to repel the opposition. The exact implications for the forces involved depend on the scenario, but what is common to all is the need to maintain a round-the-clock capability in which each individual helps to meet the demands of the operation which itself is limited only by the endurance of the hardware. Such operations may involve interdiction or long range air support, a campaign to liberate an occupied country or a carrier-borne air operation. In all these cases, and in other examples of less intensive, but nevertheless sustained activity, there is the need to meet the operational requirement, and for individuals to sustain a workload far beyond that which may have been experienced previously. It is in such scenarios that the use of drugs to ensure sleep during limited rest periods and vigilance during critical duty periods arises. A brief review of some previous military operations where hypnotics and/or stimulants have been used may be appropriate.

Royal Air Force

The Royal Air Force (RAF) used the hypnotic temazepam during the South Atlantic Campaign to regain sovereignty of the Falkland Islands,[1,2] and during the liberation of Kuwait. The South Atlantic Campaign involved long range return flights from Ascension Islands of 6,000 - 8,000 miles and during the campaign some transport crews attained 150 flying hours within 24 days. This involved six long range missions lasting up to 28 hours each. Duty extended over two nights, and the mission was achieved with augmented crews involving a pilot and navigator. Some transport crews accumulated 360 flying hours within a three month period. Crews involved in maritime reconnaissance attained 100 flying hours within 14 days with flights which varied from 6 to 20 hours, and these were also augmented with a pilot and engineer. Temazepam was used widely. The majority of aircrew took 20mg to get to sleep at various times of the day and experienced good sleep without side or residual effects. They were advised to take the hypnotic at least eight hours before flight and whenever possible were given an initial dose to assess any untoward effect, though none was encountered.

United States Air Force

The United States Air Force (USAF) has used amphetamines and caffeine in support of air operations since the early 1960s. Amphetamine was used during the Vietnam War and during the air strike on Libya in 1986.[3] During the campaign to liberate Kuwait it was used occasionally by aircrew of the USAF Tactical Air Command who deployed from the United States by air-to-air refuelling for Operations Desert Shield and Desert Storm, and up to 5mg every four hours during tactical flying operations with each dose preceding a critical stage of the flight by 30 minutes. It was considered that dextroamphetamine was a safe and effective medication which improved aircrew cockpit performance and enhanced flight safety.[4]

United States Navy

The United States Navy has a cautious attitude to the use of amphetamines, at least as far as their carrier-based air operations are concerned. In Operation Southern Watch, which from 1992 involved operations over Southern Iraq, the policy of the United States Navy precluded the use of amphetamines to maintain performance, though caffeine was acceptable using protocols developed by the Naval Aerospace and Operational Medical Institute. Caffeine tablets (100-150mg) were taken as necessary up to 300-600mg in any 6 hour period, avoiding ingestion from 24 to 48 hours pre-flight to maximise the in-flight benefit. Caffeine was considered to be extremely helpful in maintaining capability with few, if any, adverse effects.[5]

RESEARCH IN MILITARY ESTABLISHMENTS

The use, and potential use, of hypnotics and stimulants in military operations is likely to be based on experimental work carried out in research establishments which directly support the military. Studies published by such establishments are particularly revealing as they not only indicate the drugs which are of interest to a particular service, but also the circumstances in which they may be used. Hypnotics are used for critical sleep periods, while an analysis of the data available suggests that as far as stimulants are concerned there are two broad scenarios. Stimulants could be used to counteract the effects of sleep deprivation (prolonged sleep deprivation), or to avoid impaired performance over a discrete period of time within a complex pattern of work and rest – usually involving duty overnight. The published studies from military establishments world-wide will be reviewed in these contexts.

HYPNOTICS

Efficacy and Residual Effect. Studies on the efficacy and possibility of residual effects of hypnotics were carried out by the RAF Institute of Aviation Medicine during the 1970s and '80s, and temazepam was selected as the drug of choice for aircrew. A rapidly absorbed formulation and a dose of 10 or 20mg provided useful hypnotic activity with freedom from residual effects. Temazepam has been used by both military and civil aircrew in the United Kingdom for the last 20 years.[6,1,2]

Studies on temazepam (20mg) have also been carried out by the Royal Australian Army Medical Corps, Oakey, Queensland, in relation to trans-meridian travel.[7] The rate of adjustment was not affected by temazepam, but it had a beneficial effect on sleep and alertness after transmeridian travel without detrimental effects on performance. Temazepam (20mg) has also been studied in individuals coping with an acute shift of their sleep-wake cycle. Porcu, Belltreccia, Ferrara and Casagrande (1997) from the Reporto Medicina Aeronautica e Spatiale, Aeroporto Pratica di Mare, Italian Air Force,[8] studied sleepiness during the night after a daytime administration of 20mg temazepam. Temazepam was effective in inducing and maintaining sleep without any significant carry over effect.

However, it is unfortunate that temazepam has, of recent years, been subject to abuse, and for this reason the use of temazepam, at least in the United Kingdom, is now subject to various controls. It could, therefore, well be appropriate to use an alternative hypnotic free of such medico-legal restraints. In this context zolpidem is clearly a candidate to be included in aircrew medication. The studies carried out by the Service de Sante, Base Aeronavale, Rochefort Aeromarine are of interest. Sicard, Trochera, Moreau, Viellefond & Court (1993)[9] evaluated zolpidem (10mg) for its residual effects on daytime wakefulness in navy fighter pilots. The absence of residual effects showed that zolpidem could be considered for operational use. These studies supported previous assessments carried out by the RAF Institute of Aviation Medicine.[10]

The usefulness of naps with placebo and with zolpidem (10mg) has been explored by the US Army Aeromedical Research Laboratory, Fort Rucker.[11] Subjects were exposed to three separate 38 hour periods of continuous wakefulness, each separated by 10 hours for recovery sleep, and the effect of a 2 hour evening nap on subsequent performance studied. Naps with placebo and especially with zolpidem attenuated the decrements normally associated with sleep deprivation, but post-nap impairment persisted in both cases, which the authors considered could compromise performance under operational conditions.

A hypnotic with a shorter duration of action than zolpidem would, perhaps, be more appropriate for use during naps. One possibility is zaleplon, which has a duration of action of around 1 hour. However, the usefulness of this compound has not been evaluated using simulations of operational scenarios, and such studies would be required before any recommendations could be made.

STIMULANTS

Prolonged sleep deprivation. The effects of stimulants on performance during prolonged sleep deprivation have been studied by the Walter Reed Army Institute of Research (WRAIR) and the Naval Health Research Center (NHRC), by the Defence and Civil Institute of Environmental Medicine (DCIEM), and by Centre de Recherches du Service de Santé des Armées (CRSSA), the Centre d'Etudes et de Recherches de Médicine Aérospatiale

(CERMA) and the Institut de Médicine Aérospatiale du Service de Santé des Armées (IMASSA). The Walter Reed Army Institute of Research and the Defence and Civil Institute of Environmental Medicine have been concerned with the effects of amphetamine. In the study at Walter Reed[12] subjects underwent total sleep deprivation for a period of 60 hours from 0730 hours on the first day of the experiment. Dextroamphetamine sulphate (5, 10 and 20mg) was given at 0830 hours on day three after 48 hours of sleep deprivation, and performance was measured over the next 12 hours. The effect of the drug was observed during the day after loss of two nights' sleep. Amphetamine led to dose-related increases in daytime sleep latencies and cognitive performance, and significant effects were seen with 10 and 20mg. The authors concluded that amphetamine was an effective agent for the rapid alleviation of the effects of sleep loss, but advised caution in the use of amphetamines under field conditions.

In the joint studies carried out by the Defence and Civil Institute of Environmental Medicine (DCIEM) and the Centre de Recherches du Service de Santé des Armées[13] the effects of 20mg d-amphetamine and 300mg modafinil were assessed during a period of 64 hours of continuous work and sleep loss. The drugs were given at 2330 hours and 0530 hours during the first and second nights of sleep deprivation and again at 1530 hours during the third day of continuous work. Amphetamine and modafinil improved performance in a similar manner, though modafinil led to fewer side effects than amphetamine. The authors concluded that modafinil could prove to be an acceptable alternative to amphetamine in counteracting the effects of sleep loss during sustained operations. However, further studies at DCIEM[14] have suggested that modafinil (300mg), but not amphetamine (20mg), may lead to overconfidence, and so these authors advise that a comprehensive understanding of the effects of this drug should be reached before it is used operationally.

Modafinil has also been studied by the Institut de Médicine Aérospatiale (IMASSA-CERMA). Modafinil at a dose of 200mg – lower than that studied by DCIEM and CRSSA – was given on six occasions at eight hourly intervals (2200, 0600 and 1400 hours), over a period involving 60 hours sleep deprivation from 0700 hours on the first day, with the first ingestion the same day at 2200 hours. The authors[15] concluded, from both subjective and objective evidence, that satisfactory levels of vigilance had been maintained free of microsleeps. In a discussion on the activity of modafinil,[16] Lagarde and Batejat pointed out that, though modafinil has a wakening effect similar to that of d-amphetamine, it is without the adverse mood effects of amphetamine observed by Newhouse *et al.*[12] They proposed that the lack of adverse effects on mood and on the cardiovascular system indicated that modafinil may be potentially useful for maintaining efficiency during prolonged wakefulness.

More recently a study has been carried out by the United States Army Aeromedical Research Laboratory (USAARL) on the effects of modafinil on aviator performance during 40 hours of continuous wakefulness.[17] Three 200 mg doses of modafinil were given over a period of 8 hours. Modafinil attenuated the effects of sleep deprivation, but vertigo, nausea and dizziness were associated side-effects, and these were problematic during simulator flights. Simulators tend to increase motion sickness in susceptible individuals, and it could well be that some of these difficulties would subside under actual flight conditions. It is also possible that side effects would be ameliorated by lowering the drug dosage over the 8-hour period. Although the experiment did not allow direct comparisons between modafinil and dextroamphetamine, it was considered that modafinil was the less efficacious of the two, and was more likely to produce side effects.

Studies at the Naval Health Research Center have been concerned with the use of pemoline.[18] Pemoline (37.5mg) was given on four occasions separated by 12 hours, commencing at 2200 hours, during a 64 hour period without sleep. Pemoline was consistent in counteracting the effects of sleep loss and of the circadian cycle on performance, and was free of any effect on mood. An important point made by the authors is that sleep deprivation should not be the only determinant of whether, or when, to administer a stimulant. An individual deprived of sleep for 50 hours may not benefit much from pemoline when given at 1000 hours, whereas an individual with minimal sleep deprivation may well benefit when given the drug overnight. Their data suggested that pemoline may predominantly ameliorate decrements in performance which arise with the circadian cycle. These observations are relevant to the studies carried out in the United Kingdom by the Royal Air Force School of Aviation Medicine and Defence Evaluation and Research Agency on the effects of pemoline on

prolonged duty overnight[19,20] which will be reviewed later.

The potential effects of methylphenidate on performance has also been investigated by the United States Naval Health Research Center. In the same experiment which studied pemoline, the activity of 10mg methylphenidate was assessed over a 64 hour period without sleep. In this study, although pemoline showed consistent effects, many of the differences between methylphenidate and the placebo group involved subjects performing worse on the drug than on placebo. Essentially 10mg methylphenidate was not particularly effective in counteracting the effects of sleep loss together with the nadir of performance associated with the circadian cycle. Limited effects on performance would be consistent with the studies cited in references 21 and 22, that methylphenidate only enhances performance during the day when performance is impaired by preceding sleep loss. It would, therefore, appear that methylphenidate, at least at the 10mg dose, neither enhances performance overnight nor during the day, and that any effect of the drug is limited to counteracting mild impairment of performance as would occur during the day after overnight sleep loss.

Several studies have been carried out by the Walter Reed Army Institute of Research and by the Institut de Médecine Aérospatiale (IMASSA-CERMA) on the activity of caffeine in relation to prolonged sleep deprivation.

The effect of caffeine (150, 300 and 600mg/70 kg PO) was studied, using sleep onsets and subjective assessments, after 49 hours without sleep. Caffeine led to significant alerting and long lasting beneficial mood effects.[23] Batejat, Lagarde, Pradella, van Beers, Schroiff and Sarafian[24] studied the effect of single doses on psychomotor performance during 30 hours sleep deprivation, while others[25,26] studied the effects of 300mg caffeine given every 12 hours during a 64 hour period of sleep deprivation. These studies established that time release caffeine (300mg) maintained cognitive performance up to 45 hours, increased spontaneous motor activity up to 48 hours and increased daytime sleep latencies up to 64 hours.

Duty Overnight. The above studies were concerned with prolonged sleep deprivation, but stimulants are more likely to be used operationally to reduce the effects of several hours of work alone or to ameliorate the effects of sleep loss together with the circadian nadir in performance during an overnight operation. Studies relevant to these scenarios have been carried out by the Royal Air Force Institute (later School) of Aviation Medicine and the Defence Evaluation and Research Agency (DERA), and by the Army Aeromedical Research Laboratory (USAARL), the Naval Aerospace Medical Research Laboratory (NAMRL) and the Army Research Institute of Environmental Medicine (ARIEM). In the context of the possible use of stimulants these laboratories have studied several compounds including pemoline, amphetamine, tyrosine and caffeine.

Studies carried out by the Royal Air Force Institute of Aviation Medicine during the 1980s used a model of an interdictor operation, in which a squadron of aircraft with an established aircrew-aircraft ratio was required to launch a number of missions at six-hourly intervals over a period of six to nine days.[27] With this scenario it was possible to define the pattern of work and rest which would be demanded of each individual crew. Essentially, each pattern of work was a random mix of duty periods varying between 6 and 18 hours and rest periods of 6 hours. The rest periods were critical, but even if it was assumed that each rest period provided good sleep (with or without the use of hypnotics) it was clear that some duty periods would involve low levels of performance. These were periods which involved duty of 12 to 18 hours overnight.

It was predicted from this model that, assuming the crew obtained refreshing sleep during each limited but critical rest period of six hours, about 15 interdictor missions could be operated over a nine day period, but that three or four of the overnight missions would involve low, and probably unacceptable, levels of performance. No doubt comparable scenarios could be obtained from land and sea operations, but, essentially, it is the effect of the adverse juxtaposition of many hours on duty and the circadian fall in performance overnight which is likely to lead to poor performance.

It is, therefore, in the context of sustaining air operations overnight that the question of the use of stimulants is most likely to arise. However, it must be borne in mind that the use of stimulants, as opposed to the use of hypnotics, modulates the individual while carrying out the task, and it is vital to ascertain that the stimulant does not itself give rise to unacceptable adverse effects. With the use of stimulants an attempt is made to maintain

vigilance at levels which exist during the day, and to avoid an excessive increase in arousal or adverse effects on cognition or mood which could impair the integrity of the individual.

During the 1980s the Royal Air Force Institute of Aviation Medicine attempted to establish which chemical entities would be most likely to be useful as stimulants. It was considered that stimulants whose activity was predominantly due to modulation of the noradrenergic or serotonergic systems were likely to be unsuitable in critical situations, as these drugs may give rise to unacceptable changes in cognition and mood. Suppression of REM sleep in man, independent of any reduction due to increased wakefulness, was used to exclude those drugs whose activity was likely to be predominantly noradrenergic or serotonergic, as modulation of these systems is known to suppress REM sleep in addition to any reduction induced by an alerting effect. The studies showed that drugs which did not suppress REM sleep (other than by increasing wakefulness) were unlikely to be noradrenergic or serotonergic in action,[28] and so for this reason the dopamimetic agent, pemoline, was assessed.

Turner and Mills showed that pemoline had the potential to sustain alertness and performance during work periods which involved continuous high workload overnight. Pemoline (30 and 40mg) had prolonged effects extending beyond the 12 hour period of duty, though 20mg maintained performance between 8 and 12 hours and was less likely to disturb any recovery sleep.[19] In further studies,[20] the dose range was extended down to 10mg. The study involved a 12 hour period of work during which subjective alertness and performance on a range of tasks were assessed at 1.5 hour intervals after ingestion at 2000 hours of pemoline (10, 20, 30 or 40mg). Work was preceded by a 6 hour rest period with temazepam (20mg) and was followed by 4 hour recovery rest without medication. Pemoline increased alertness and performance. With 30 and 40mg the onset of activity was delayed to 4.5 hours after drug ingestion and, again, the alerting effects persisted beyond the work period and disturbed recovery sleep. However, 10 and 20mg pemoline had no effect on recovery sleep. It was concluded that 20mg was likely to be the most suitable dose of pemoline for maintaining nocturnal performance. This dose was without adverse effects on recovery sleep and could be useful in the management of impaired performance overnight.

The Army Aeromedical Research Laboratory[29] studied the performance of helicopter pilots during simulated flights which commenced at 0100, 0500, 0900, 1300 and 1700 hours. Dextroamphetamine 10mg was given one hour before the first three assessments, which took place at 0100, 0500 and 0900 hours. Performance was improved during the 0500 and 0900 hours flights, though no effect was established at the 0100 hours flight. The study is of significance as it shows a useful effect of amphetamine when a relatively short period of sleep deprivation (say 6-7 hours) coexists with the nadir of circadian performance, and so is particularly relevant to the studies at references 18 and 20.

Amphetamine and tyrosine have also been studied by the Naval Aerospace Medical Research Laboratory.[30] In the studies with amphetamine a nine hour planning session was followed by four hours of rest and a 14 hour mission, and this was repeated after a six hour period of rest. A dose of 10mg (administered as 10mg/70kg) was given just over four hours into the second 14 hour session at 2035 hours. Amphetamine reduced fatigue without euphoria, improved performance, and lessened the tendency to shift from a conservative to a risky response strategy. The same laboratory studied the effects of tyrosine during a continuous period of night work. The study commenced at 1930 hours and ended the next day at 0820 hours. At 0130 hours the subjects were given 150mg/kg tyrosine which led to an amelioration of the decline in performance. There were useful effects on psychomotor skills, on vigilance and on monitoring functions, and ingestion was free of adverse effects on mood or on the cardiovascular system.

The UK Defence Evaluation and Research Agency Centre for Human Sciences has recently studied the efficacy of caffeine (300mg) in sustaining performance during prolonged duty overnight (unpublished data), in an experimental design in which performance was studied from 1500 hours to 0900 hours the next day, preceded by a 6 hour period of sleep with either placebo or temazepam (20mg). The ingestion of caffeine at midnight sustained performance throughout the remaining part of the night. The effect of caffeine was similar to that seen in other studies with monoaminergic compounds.

The studies on the activity of various stimulants on both prolonged sleep deprivation and duty overnight have established that many compounds

reduce the adverse effects of sleep loss and of the nadir of circadian activity on performance. Amphetamine, modafinil and pemoline in appropriate doses are probably equally effective. The choice of drug does, therefore, appear to depend on the adverse effects of the compound at the appropriate dose rather than on the primary activity of the drug itself. Many workers have cautioned against the use of amphetamine due to its effects on mood and the cardiovascular system. However, adverse effects are unlikely with the low dose (5mg) of amphetamine which has been used in air operations by the United States Air Force, though it must be borne in mind that experimental studies have raised the question whether such a low dose actually improves performance. Certainly 20mg amphetamine would appear to be high, so perhaps 10mg is the optimum dose. The balance between effectiveness and adverse effects may well favour modafinil, though questions have been raised concerning overconfidence after ingestion of this drug. At the time of writing modafinil has not been studied widely, and so the final decision must await further studies.

Pemoline (10-20mg) would appear to be a useful compound, possibly like modafinil, free of effects on mood, though it is unfortunate that hepatotoxicity in children has led to it being withdrawn in the United Kingdom, though not in the United States. With occasional use in intensive and sustained operations, the risk of hepatotoxicity appears to be remote, and so pemoline remains a candidate for occasional use in alleviating the effects of sleep loss or of the circadian nadir of performance. Studies in two countries (the United States and the United Kingdom) are encouraging. Pemoline is believed by the author to be particularly appropriate as it is dopamimetic, rather than noradrenergic or serotonergic, in action. In this context it would be of interest if the activity of modafinil were also shown to be primarily on the dopamimetic system.

Caffeine in an appropriate formulation would appear to be a most promising stimulant both in sleep deprivation and in maintaining performance during prolonged duty overnight. It could well be that caffeine will prove to be the drug of choice.

CONCLUSION

It is evident that hypnotics and stimulants have an important part to play in sustaining personnel during intensive air operations. They have a complementary role in ensuring sleep during critical and limited rest periods, and in preserving vigilance under conditions which will inevitably involve impaired performance. As far as hypnotics are concerned, temazepam has been used for many years, but in view of the constraint imposed by medico-legal regulations on handling the drug, zolpidem may well become the hypnotic of choice. The choice of a stimulant for air operations is less clear. Amphetamine, despite concerns about its adverse effects on mood, has been used successfully, and pemoline and modafinil are clearly useful drugs. However, it could well be that caffeine proves to be the most appropriate stimulant for military operations.

The Working Group has not reviewed policy on the use of hypnotics and stimulants in air operations, and has not assessed the evaluation of the military effectiveness of any such policies.

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